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Mannitol

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Mannitol may be useful clinically both as a diuretic and as an obligate extracellular solute. As a diuretic it can be used to treat patients with intractable edema states, to increase urine flow and flush out debris from the renal tubules in patients with acute tubular necrosis, and to increase toxin excretion in patients with barbiturate, salicylate or bromide intoxication. As an obligate extracellular solute it may be useful to ameliorate symptoms of the dialysis disequilibrium syndrome, to decrease cerebral edema following trauma or cerebrovascular accident, and to prevent cell swelling related to renal ischemia following cross-clamping of the aorta. Largely unexplored uses for mannitol include its use as an osmotic agent in place of dextrose in peritoneal dialysis solutions, its use to maintain urine output in patients newly begun on hemodialysis, and its use to limit infarct size following acute myocardial infarction.

MANNITOL IS A 6-carbon alcohol with a molecular weight of 182, prepared commercially by the reduction of dextrose. Although it has an important place in current therapy, few physicians fully understand its chemistry, mode of action or clinical applicability. Since 1940, when Smith and associates[1] showed that mannitol clearance closely reflected glomerular filtration rate in man, there has been clinical interest in mannitol. However, recent emphasis on the role of cell swelling in the genesis of ischemic tissue damage has rekindled awareness of the medical uses of mannitol as more than only an osmotic diuretic.

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Pharmacokinetics

Because orally administered mannitol is not absorbed, it must be administered parenterally. It distributes almost entirely in the extracellular fluid, very little penetrating cells. As a result, it is virtually inert, only 7 percent to 10 percent being metabolized, probably in the liver, while the rest is freely filtered by the glomeruli and excreted intact in the urine. About 7 percent is reabsorbed by the renal tubules. With normal kidney function, after a single intravenous dose, the half-life of mannitol in the circulating plasma is 15 minutes.[2] Of an injected dose, 90 percent is recovered in the urine after 24 hours.[3] However, with severe renal insufficiency the rate of mannitol excretion is greatly reduced and retained mannitol may increase extracellular tonicity leading to a shift of water out of cells, expanding the extracellular

fluid as well as inducing an apparent hyponatremia with increased serum osmolality such as occurs in hyperglycemia. Therefore, mannitol should be used cautiously under these conditions.

Physiological Effects

Renal

Osmotic diuretics are obligate solutes of low molecular weight, which are freely filtered at the glomerulus and poorly reabsorbed by the renal tubules. The resulting high urinary concentration profoundly affects renal water and sodium reabsorption. An almost ideal prototype, mannitol was used extensively in early physiological studies of osmotic diuresis. Wesson and Anslow[4] concluded that the proximal tubule was the primary site of action of mannitol's osmotic diuretic effect. More recently, however, Seely and Dirks[5] have precisely defined this phenomenon, their work being confirmed later by others.[6] Using micropuncture techniques, they elegantly demonstrated that half the effect of mannitol occurs proximally and half occurs in the ascending limb of the loop of Henle and proposed the following mechanism: The osmotic effect of mannitol depresses proximal reabsorption of water more than sodium, thereby decreasing proximal tubular fluid sodium concentration. Consequently, the gradient for passive sodium reabsorption in the thin ascending limb of the Henle loop is decreased. The natriuresis of mannitol diuresis, therefore, results largely from decreased sodium reabsorption in the loop of Henle. In addition, changes in medullary tonicity secondary to a mannitol augmentation of medullary blood flow may also effect sodium excretion.[7] As sodium delivery to distal tubular exchange sites increases, potassium excretion may rise during mannitol diuresis.

The effect of mannitol on renal hemodynamics may be both direct and indirect. Ternes and coworkers[8] showed that there was a dose dependent increase in renal vascular resistance in isolated perfused dog renal artery strips exposed to varying perfusate concentrations of mannitol. In contrast, others[9-11] found there to be an increase in total renal blood flow *in vivo* in animals, independent of the plasma volume increase. No comparable data for humans are available.

Lilien[12] reported a biphasic dose related response in rats, which might provide a unified view of the mannitol effect on renal hemodynamics. At lower doses, there is definite vasodilatation probably mediated through efferent arteriolar dilatation, which could also contribute to the slight decrease in glomerular filtration rate during mannitol infusions. Conversely, at higher doses, the vasoconstrictor effect reported by Ternes and associates[8] supervenes.

Glomerular filtration rate falls slightly in animals and humans given mannitol. When mannitol is present in the proximal nephron and prevents, through its osmotic effect, sodium and water reabsorption, filtrate volume and pressure in this nephron segment rise. It is this increased intratubular pressure after mannitol administration that decreases glomerular filtration rate by Starling's law. Efferent arteriolar dilatation after mannitol is administered may occur (as has been mentioned) and may also play a role in the decreased glomerular filtration rate.

When proximal tubular sodium reabsorption is inhibited for any reason, calcium excretion in the urine increases. The precise mechanism of this coupling of sodium and calcium excretion is unknown. Even though, as explained above, decreased proximal tubular sodium reabsorption does not account for the bulk of the natriuresis after mannitol administration, the amount of sodium escaping proximal tubular reabsorption is increased. As a result, calcium excretion increases proportionately.[13,14] Independent of the natriuresis, urinary phosphate excretion also increases during mannitol diuresis.[15]

The only renal histologic effect of mannitol infusions in animals[16] or humans[17] is the same reversible proximal tubular cell vacuolization reported after sucrose and other osmotic diuretics. However, it is not associated with any functional tubular defects.

Cardiovascular

Intravenously injected mannitol is confined to the extracellular fluid space. The increased tonicity obligates water to move from the intracellular to the extracellular fluid to maintain osmotic equilibrium. With each 182 mg per dl increase in mannitol concentration, a 10 milliosmole increase in extracellular fluid osmolality occurs with the same proportionate dilution of all serum electrolytes as occurs in hyperglycemia. Various amounts of plasma volume expansion have been reported with mannitol infusion ranging from 1 ml per kg of body weight per 5 grams of mannitol infused[18] to 3 ml per kg of body weight per 5 grams of

mannitol infused,[19] depending on body osmolarity and the relationship among plasma volume, extracellular fluid and total body water in the individual animal or person. With each 100 mg per dl increase in mannitol concentration in the extracellular fluid, serum sodium falls 1.6 to 2.6 mEq per liter.

After the expansion of the extracellular fluid and blood volume by injection of mannitol mean arterial pressure,[20,21] cardiac output,[20,21] heart rate,[21,22] coronary blood flow[20] and left ventricular end diastolic pressure[22] all increase. In isolated perfused artery segments, physiologic doses of mannitol cause vasodilatation and block the vasoconstrictor effects of norepinephrine.[23]

Cerebrovascular Disease

Mannitol has several physiologic effects on the cerebrovascular system. Increased cerebral blood flow,[24] increased cerebral oxygen consumption[24] and decreased cerebrospinal fluid pressure[24,25] have all been documented. The decreased cerebrospinal fluid pressure, in spite of increased cerebral blood flow, is of interest. Since mannitol cannot cross the blood brain barrier, it causes water to move out of the brain into the extracellular fluid. This decrease in brain water is the cause of the fall in cerebrospinal fluid pressure. The movement of water out of the brain in response to the osmotic effect of mannitol decompresses the brain when cerebral edema is present. It is more effective than urea in this regard since urea slowly crosses the blood brain barrier and therefore maintains a lower osmotic gradient for water movement out of the brain.

Ocular System

Mannitol profoundly lowers intraocular pressure when given intravenously[26,27] just as it lowers cerebrospinal fluid pressure. In addition, when applied topically to the cornea mannitol may be absorbed and also have an ocular hypotensive effect.[28]

Concept and Importance of Cell Swelling

In a variety of organs, including kidney, heart and brain, following relatively brief periods of vascular occlusion, reperfusion fails to restore normal circulation.[29,30] This phenomenon of impaired reflow is caused by vascular endothelial cell swelling induced by the ischemic anoxia. Normally, the diffusion of sodium into and of potassium out of cells down existing concentration gradients is opposed by a *pump* requiring energy from oxidative metabolism, which constantly moves sodium out of cells and potassium into cells against the concentration gradients. During hypoxia the metabolic energy required by this pump which normally extrudes sodium from cells is lacking. As a result, sodium accumulates intracellularly. To maintain osmotic equilibrium, water shifts in, swelling the endothelial cell, impairing the flow of blood. Following prolonged depression of blood flow, tissue death results. However, if flow can be restored in time, reversal of the ischemic injury can occur. Restoration of flow, which is dependent upon the removal of intracellular water with consequent shrinking of endothelial cells to normal size, can be readily accomplished by the intravenous administration of hypertonic mannitol solutions to increase extracellular fluid osmolality.

Clinical Uses

Diuretic

Being an obligatory solute, mannitol may be used either as an osmotic diuretic per se to maintain water excretion or potentiate the action of saluretic diuretics (see below). In the clinical edemas of severe nephrotic syndrome,[31] cirrhosis with ascites[32] or congestive heart failure, conventional diuretics, for example, the loop diuretics, may not promote much diuresis partly because of greatly increased proximal tubular reabsorption of sodium and water caused by ineffectively circulating volume. Under these circumstances, mannitol, by reducing proximal tubular reabsorption of sodium and water, increases the sodium load reaching the more distal tubular segments, enhancing the effect of the saluretics. Because enhanced distal nephron sodium reabsorption may quantitatively play a greater role in sodium retention in these conditions, however, the use of mannitol alone might not be sufficient to produce the desired diuresis.

Clinically, mannitol has also been used to treat severe water overload and hyponatremia. In these situations, the hyponatremia is dilutional. The osmotic effect of mannitol in the urine, as discussed earlier, causes a diuresis with an excess of water over electrolytes being excreted. By administering 25 gram boluses of hypertonic mannitol intravenously hourly, as needed to maintain urine flow, water excretion can be notably augmented. Each 5 grams of mannitol ultimately

leads to excretion of approximately 100 ml of water in excess of electrolyte, and serum sodium will rise. Thus, massive water diuresis with rapid correction of the hyponatremia follows intravenous infusion of hypertonic mannitol. However, in patients with existing intravascular volume overload or with severe myocardial disease, such infusions may excessively expand intravascular volume producing pulmonary congestion or frank pulmonary edema.

Prevention of Acute Renal Failure

Although some have questioned whether mannitol administration may prevent the development of ischemic acute renal failure (ARF),[33,34] considerable experimental and clinical data support this prophylactic application.[35-46] The reduction in ischemic injury to the kidneys of rats and dogs by prophylactic or early mannitol infusions is well documented.[35-40] For example, in rats mannitol infused at the time of initiation of ischemia not only increased renal blood flow[36] but also significantly decreased cell swelling and the resultant rise in blood urea nitrogen and creatinine.[35] However, in dogs, the renal failure following hemorrhagic hypotension has been reported to be unaffected by mannitol in one study,[37] whereas others have shown there to be significant increases in creatinine and para-aminohippurate clearances (glomerular filtration rate and renal blood flow) when mannitol was given before hypotension was induced.[38-40]

The benefit of mannitol in human ischemic renal disease is suggestive, if not conclusive. In 37 patients in whom oliguria developed in the absence of intravascular volume depletion, Luke and co-workers[41] infused 100 ml of a 20 percent mannitol solution intravenously over 10 to 30 minutes and measured urine output. If the output reached 50 ml per hour over the next two hours, no further mannitol was given. If the output increased, but less than 50 ml per hour, the same dose was repeated. By this technique, responders and nonresponders to mannitol could be identified. The responders subsequently had oliguria for less than 50 hours and urine-to-plasma osmolality ratios greater than 1.05, and renal failure did not occur. This strongly suggested that the mannitol infusion either identified the nonresponders as patients who would progress to renal failure or was able to reverse the developing renal failure in the responders as reported by Eliahou.[47] Similarly, in a variety of toxin or pigment induced renal failure in animals,[42,43] mannitol, if given early, has been shown to ameliorate or to prevent renal failure. Finally, Dawson[45,46] has reported extensive experimental and clinical evidence that the severe acute tubular necrosis (ATN) which may complicate the postoperative course of hyperbilirubinemic patients may be prevented by establishing and maintaining mannitol diuresis until serum bilirubin concentration has fallen to an acceptable level.

In summary, the evidence in animals and humans is highly suggestive that mannitol, either by decreasing glomerular capillary endothelial cell swelling and thus restoring glomerular blood flow; decreasing proximal tubular cell swelling and promoting movement of intratubular debris[48] that could be causing tubular obstruction; diluting urine and washing out toxin; or improving renal perfusion, can ameliorate or prevent development of acute renal failure from a variety of causes. In oliguric patients with repleted intravascular volume we recommend the following mannitol trial:

- Rapidly inject 12.5 to 25 grams of 20 percent to 25 percent solution of mannitol intravenously and measure urine volume and specific gravity hourly.
- If urine output in the next hour is less than 50 ml repeat the same dose.
- If still no response, established acute renal failure is present and no more mannitol should be given.
- If the patient responds, either incipient acute renal failure has been reversed or oliguric acute renal failure has been converted to nonoliguric, either of which has a better prognosis than oliguric acute renal failure. Underlying pathogenetic factors— for example, extracellular fluid depletion— should be corrected.
- Be aware of possible complications of mannitol therapy (see below).

Dialysis

Dialysis disequilibrium is a common complication of rapid, efficient hemodialysis. Manifestations of this syndrome include nausea, vomiting, headache, blurred vision and seizures all caused by brain swelling and increased intracranial pressure. Dialysis induced hypotension (in the absence of volume depletion) and muscle cramps are also felt by many[49,50] to be part of this syndrome.

Most symptoms result from brain and muscle cell swelling due to water shifts following rapid removal of solute from the intravascular space with resultant disruption of the normal intracellular-extracellular fluid osmotic equilibrium. The relation of dialysis induced hypotension to osmolality changes remains to be defined. Hagstam and coworkers[49] and Rodrigo and associates[50] showed that many features of this syndrome can be prevented by infusing hypertonic mannitol into the venous return line of the dialyzer continuously during dialysis. In functionally anephric patients, however, mannitol should be used for only the first few dialyses or intermittently when severe symptoms related to disequilibrium occur[50] to avoid mannitol accumulation in the extracellular fluid.

Mannitol has two other possible uses in dialysis. First, it may be added to peritoneal dialysate to increase the osmolality, thus promoting fluid removal, particularly in diabetic patients who become severely hyperglycemic after continued use of conventional hypertonic glucose peritoneal dialysate. Second, mannitol infusions might be given to maintain osmotic load and urine output after dialysis preventing virtual anuria in patients undergoing hemodialysis or peritoneal dialysis therapy. Maintaining some urine flow would aid in fluid management and promote some potassium excretion in these patients. The later use for hypertonic mannitol has not been adequately tested, however.

Renal Transplantation

Mannitol may be administered safely to patients with renal transplants to distinguish post-transplant acute tubular necrosis and acute rejection. Anderson and associates[51] carried out studies in five renal transplant patients with previous bilateral nephrectomies, who were oliguric following transplantation. Acute rejection eventually was found in four of the five in whom diuresis occurred after injections of mannitol and ethacrynic acid.

Diagnostic Tool

Mannitol has been used to diagnose renal disease unrelated to acute renal failure. Mannitol pyelography may be used to visualize renal collecting structures not seen on routine intravenous pyelogram because of high blood urea nitrogen,[52] as well as to magnify the intravenous pyelogram abnormalities associated with unilateral renal artery stenosis.[50] Similarly, partial versus complete and central versus renal diabetes insipidus[54] may be distinguished by comparing the change in free-water clearance (CH_2O) in response to infusion of hypertonic mannitol alone (which stimulates antidiuretic hormone release and decreases free water clearance) in contrast to infusion of mannitol plus antidiuretic hormone to see if the response to mannitol can be augmented. The details are nicely outlined by Oetliker and associates.[54]

Toxin Excretion

Mannitol infusion has been used extensively in prophylatic and active treatment of intoxications with endogenous and exogenous substances whose clearance is increased by mannitol.[55] Rapid excretion of secobarbital,[55] eucalyptus oil,[56] salicylates[57] and bromides[58] has been reported after mannitol administration. In addition, endogenous substances such as uric acid,[59,60] hemoglobin and myoglobin are rapidly excreted without renal damage after mannitol administration. Mannitol may also modify or prevent the nephrotoxicity of certain chemotherapeutic agents. This has been clearly shown for cis-platinumdisamminedichloride[61,62] and is suggestive for tetracyline[63] and amphotericin B.[64-66]

Cerebrovascular Disease

Because cerebral edema or intracranial pressure is reduced following rapid infusion of 20 percent mannitol solution, this technique has been widely used in treating cerebrovascular diseases including postangiography brain swelling,[67] Reye syndrome,[68] hypoglycemia,[69] trauma[70,71] and the cerebral edema following neurosurgery,[72,73] as well as dialysis disequilibrium. A 20 percent to 50 percent reduction in intracranial pressure 30 to 45 minutes after mannitol administration has been noted. This effect may last up to several hours. A small rebound in pressure is then noted,[74] but this is much less than that seen after urea administration. An analagous effect of mannitol on spinal cord pressure after trauma in cats has been noted,[75] suggesting that mannitol may be used to decrease spinal cord swelling after trauma, surgical operation or irradiation. Whether mannitol can promote resorption of chronic subdural hematomas has been disputed[76,77] and at present is unsettled. Finally, there is a suggestion that

mannitol can alter the blood brain barrier and increase the entry of intravenously administered antibiotics into the central nervous system.[78]

Cardiovascular Disease

Oliguria with decreased glomerular filtration rate and renal plasma flow commonly occurs following open heart surgical procedures under cardiopulmonary bypass. The mechanisms are not fully understood but may reflect a degree of acute renal failure. Mannitol given either intravenously or as a prime for the bypass pump, may decrease the magnitude and severity of these changes.[79,80] In patients in whom aortic operations are done with cross-clamping of the aorta below the renal arteries, analogous changes develop in renal function, which are also prevented by intravenous mannitol given just before cross-clamping.[81] Finally, more recently the protective effect of mannitol on ischemic myocardium has been intensively studied. When given to animals just before experimental coronary artery occlusion, mannitol decreases cell swelling, water content and necrosis in anoxic myocardial cells.[82-90] It increases total and collateral myocardial blood flow, reduces electrocardiographic evidence of ischemia, decreases coronary vascular resistance and increases cardiac output. However, such administration of mannitol after coronary occlusion has not limited infarct size, and the role of mannitol therapy in human coronary artery disease remains to be elucidated.

Miscellaneous Uses

Mannitol has been used to decrease pulmonary vascular resistance and increase alveolar ventilation in the acute respiratory distress syndrome,[91] to terminate pregnancies,[92] to stop hematuria as-

TABLE 1.—*Clinical Applications of Intravenously Given Mannitol Solutions*

I. Diagnostic Evaluation of Acutely Oliguric Patient
   A. Test dose of 12.5 to 25 grams mannitol (20 percent to 25 percent solution) should be given in intravenous push over three to five minutes.
   B. If no response (>50 ml urine/hour) repeat the same dose in one hour.
   C. If still no response, no further mannitol should be given and treatment for acute tubular necrosis instituted.

II. Therapeutic Uses
   A. Prevention of acute renal failure (such as after cardiovascular surgical operation)
      1. Test dose as above followed by a priming dose of sufficient concentrated (20 percent) mannitol over an hour to bring the priming dose to 50 grams.
      2. Maintain urine output at 50 ml/hour with intravenous infusion of 5 percent mannitol plus 20 mEq sodium chloride/liter and 1 gram calcium gluconate/liter. Later, if needed, appropriate concentrations of potassium acetate, magnesium sulfate and more sodium chloride should be given as indicated.
   B. Treatment of Oliguria
      1. Test dose as above.
      2. If response is noted, look for underlying cause of oliguria other than acute tubular necrosis, for example, hypovolemia due to subtle cause of extracellular fluid contraction, such as third spacing.
   C. Adjunctive Therapy for Intoxications
      1. Test dose as above followed by priming dose (IIA).
      2. Maintain urine output at 150 to 500 ml/hour with a continuous intravenous infusion of 5 percent mannitol, each liter containing 45 mEq sodium chloride, 24 mEq sodium acetate, 1 gram calcium gluconate, 1 gram magnesium sulfate and 20 mEq potassium acetate. If alkalinization of the extracellular fluid and urine is desired as in treatment of barbiturate intoxication less sodium chloride and more sodium acetate may be given depending on hourly checks of urine pH or blood gases. Serum electrolytes and osmolarity should be monitored periodically.
   D. Treatment of Elevated Intracranial or Intraocular Pressure
      1. 100 to 150 grams (15 percent or 20 percent solution) given over 30 to 60 minutes. Repeat as necessary to control intracranial or intraocular pressure.
      2. Use 60 to 90 minutes before craniotomy or ocular surgery for maximal effect.
   E. Treatment of Water Intoxication With Symptomatic Dilutional Hyponatremia
      1. Test dose followed by a priming dose as above (IIA).
      2. Give 20 percent mannitol as 25 gram boluses hourly or by continuous infusion at a rate of 100 to 125 ml per hour.
   F. Potentiation of Diuresis in Patients With Intractable Cardiac, Cirrhotic and Nephrotic Edema
      1. Give intravenous injection of near maximal dose of ethacrynic acid or furosemide.
      2. Follow immediately with test dose of mannitol as described above followed by slow intravenous infusion of 10 percent to 20 percent mannitol at a rate of 50 to 75 ml/hour.
      3. Patient's cardiovascular status including central venous pressure, urine output and osmolarity and serum electrolytes should be carefully monitored during the infusion.

sociated with sickle cell trait[93] and to augment iodine 131 uptake in the treatment of thyroid cancer.[94]

Administration

Specific recommendations for intravenous administration of mannitol are presented in Table 1 for each of several clinical applications.

Precautions

One case report of an allergic reaction associated with mannitol administration has been published.[95] However, the relationship is unclear since mannitol is inert and no other cases have been reported. On the other hand, in a patient with poor renal function and incipient heart failure, excessive volume expansion following mannitol infusion can be a serious side effect and mannitol should be administered very cautiously in such a situation. After hypertonic mannitol administration, particularly of bolus doses,[96] dilutional hyponatremia and cellular dehydration may result from the movement of water out of cells in response to increased extracellular fluid tonicity. In a patient with good renal function this abnormality is of little consequence and is rapidly corrected as mannitol is excreted. In a patient with poor kidney function, however, sustained hyperosmolality, hyponatremia and cellular dehydration may be serious complications.[97] Rarely, hypernatremia and dehydration from excessive water loss in response to larger rapid infusions of hypertonic mannitol in patients with functioning kidneys, and occasionally mild hyperkalemia of unclear origin,[98] may occur. Finally, in uremic dogs given mannitol pronounced decreases in cerebrospinal fluid pH resulting in death have been noted.[99] Similar changes in cerebrospinal fluid pH in human beings with uremia after mannitol administration have not been studied.

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